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BIOASSAY OF FENTHION FOR POSSIBLE CARCINOGENICITY

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Carcinogenesis Testing Program
Division of Cancer Cause and Prevention
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BIOASSAY OF
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Carcinogenesis Testing Program
Division of Cancer Cause and Prevention
National Cancer Institute
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FOREWORD: This report presents the results of the bioassay of fenthion conducted for the Carcinogenesis Testing Program, Division of Cancer Cause and Prevention, National Cancer Institute (NCI), National Institutes of Health, Bethesda, Maryland. This is one of a series of experiments designed to determine whether selected environmental chemicals have the capacity to produce cancer in animals. Negative results, in which the test animals do not have a greater incidence of cancer than control animals, do not necessarily mean that the test chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of circumstances. Positive results demonstrate that the test chemical is carcinogenic for animals under the conditions of the test and indicate that exposure to the chemical is a potential risk to man. The actual determination of the risk to man from chemicals found to be carcinogenic in animals requires a wider analysis.

CONTRIBUTORS: This bioassay of fenthion was conducted by Gulf South Research Institute, New Iberia, Louisiana, initially under direct contract to NCI and currently under a subcontract to Tracor Jitco, Inc., prime contractor for the NCI Carcinogenesis Testing Program.

The doses for the chronic study were selected by Drs. E. E. Storrs (1) and O. G. Fitzhugh (2,3). The principal investigator was Mr. R. J. Wheeler (1). Chemicals were analyzed by Mr. Wheeler and dosed feed mixtures by Mr. S. M. Billedeau (1). The results of these analyses were reviewed by Dr. C. W. Jameson (2). Histologic examination of animal tissues was performed by Drs. R. A Ball (1) and B. Buratto (1), and the diagnoses included in this report represent the interpretation of these pathologists.

Animal pathology tables and survival tables were compiled at EG&G Mason Research Institute (4). Statistical analyses were performed by Dr. J. R. Joiner (2) and Ms. P. L. Yong (2), using methods selected for the bioassay program by Dr. J. J. Gart (5).

This report was prepared at Tracor Jitco (2) under the direction of NCI. Those responsible for the report at Tracor Jitco were Dr. L. A. Campbell, Director of the Bioassay Program; Dr. S. S. Olin, Deputy Director for Science; Dr. J. F. Robens, toxicologist; Dr. R. L. Schueler, pathologist; Dr. G. L. Miller, Mr. W. D. Reichardt, and Ms. L. A. Waitz, bioscience writers; and Dr. E. W. Gunberg, technical editor, assisted by Ms. Y. E. Presley and Ms. P. J. Graboske.

The following scientists at NCI (6) were responsible for evaluating the bioassay experiment, interpreting the results, and reporting the findings: Dr. Kenneth C. Chu, Dr. Cipriano Cueto, Jr., Dr. J. Fielding Douglas, Dr. Richard A. Griesemer, Dr. Thomas E. Hamm, Dr. William V. Hartwell, Dr. Morton H. Levitt, Dr. Harry A. Milman, Dr. Thomas W. Orme, Dr. Sherman F. Stinson, Dr. Jerrold M. Ward, and Dr. Carrie E. Whitmire.

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SUMMARY

A bioassay of fenthion for possible carcinogenicity was conducted by administering the test chemical in feed to F344 rats and B6C3F1 mice.

Groups of 50 rats of each sex and 50 mice of each sex were administered fenthion in the diet at one of two doses, either 10 or 20 ppm, for 103 weeks and then observed for 0 to 2 additional weeks. Matched controls consisted of groups of 25 untreated animals of each species and sex. All surviving animals were killed at 103 to 105 weeks.

The mean body weights and the survivals of the dosed animals were essentially unaffected by administration of the test chemical with the exception of the survival of the low-dose male mice, which was significantly lower than that of the corresponding matched control. Thus, most of the animals may have been able to tolerate higher doses. Sufficient numbers of animals in all groups of rats and mice were at risk for development of late-appearing tumors.

In the male and female rats and the female mice, no tumors occurred at incidences that were significantly higher in dosed groups than in control groups.

In the male mice, sarcomas, fibrosarcomas, or rhabdomyosarcomas of the integumentary system occurred at incidences that were dose related ($P = 0.043$). In direct comparisons of the incidences of these tumors in the dosed groups with the incidence in the control group, the P values of 0.048 and 0.028 for the low- and high-dose groups, respectively, did not meet the Bonferroni criterion of $P = 0.025$ for significance when multiple comparisons are made (controls 0/25, low-dose 7/49 or 14%, high-dose 8/48 or 17%). However, the incidence of sarcomas and fibrosarcomas in historical-control male B6C3F1 mice used in bioassays of other chemicals tested at this same laboratory was 7/435 (1.6%), and no rhabdomyosarcomas occurred in the historical-control male mice.

It is concluded that under the conditions of this bioassay, fenthion was not carcinogenic for male or female F344 rats or for female B6C3F1 mice. The increased incidence of sarcomas, fibrosarcomas, and especially rhabdomyosarcomas of the integumentary system in the male B6C3F1 mice suggested that the test chemical was carcinogenic in these animals.

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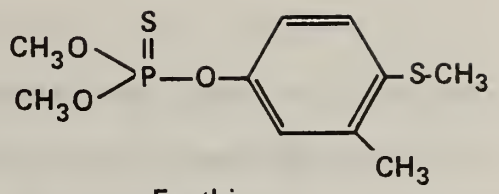
I. INTRODUCTION

Fenthion (CAS 55-38-9; NCI C08651), the O,O-dimethyl ester of O-(4-(methylthio)-m-tolylphosphorothioic acid, is one of the organophosphate pesticides. It was developed by G. Schrader and E. Schegk and first marketed by Farbenfabriken Bayer A.G. as an insecticide in 1957 (Spencer, 1973). This organophosphorus pesticide inhibits the enzyme cholinesterase, thereby preventing the hydrolysis of acetylcholine in insects and mammals. The effects of the excessive accumulation of acetylcholine may be lethal to humans if not treated (Murphy, 1975).



Fenthion

In recent years, this insecticide has been used in California for the control of mosquitoes which are vectors of encephalitis (Ayers and Johnson, 1976). Approximately 200,000 pounds of fenthion were used in the United States in 1974, and an analysis of use patterns showed that virtually all of the chemical was sprayed over wetlands for insect control (Ayers and Johnson, 1976).

Fenthion is also applied topically to control warble grubs and lice in beef and non-lactating cattle (Food and Drug Administration, 1976), and it has been used for insect control in food handling establishments (Environmental Protection Agency, 1973).

The acute oral LD_{50} for fenthion has been reported as 260 mg/kg in the Sprague-Dawley male rat, 325 mg/kg in the Sprague-Dawley female rat, 125 mg/kg in the CF_1 male mouse, and 150 mg/kg in the CF_1 female mouse (DuBois and Kinoshita, 1964).

In other studies, fenthion given orally to male rats (strain not specified) at 30 mg/kg for 13 weeks caused approximately 30% mortality (Kimmerle, 1961), and when fed to male and female rats (strain not specified) at 0.25-5.0 mg/kg for 3 months induced mortality (percent not given) in the females at 5.0 mg/kg (Shimamoto and Hattori, 1969). Metabolic products of fenthion (sulfoxide, sulfone, oxygen analog, O-sulfoxide, and O-sulfone) were found to be toxic in albino, Porton strain male rats by oral administration (Francis and Barnes, 1963).

Fenthion was selected for study in the Carcinogenesis Testing Program as a part of efforts to assess the carcinogenic potential of certain pesticides.

II. MATERIALS AND METHODS

A. Chemical

Technical-grade fenthion was obtained in a single batch (Lot No. 4050284) from the Chemagro Division of Mobay Chemicals, Kansas City, Missouri, and used during all phases of testing. Elemental analyses for C, H, S, and P were consistent with $C_{10}H_{15}O_3PS_2$, the molecular formula of fenthion. Thin-layer chromatography showed a single spot. Gas-liquid chromatography (flame ionization detector) showed no impurities. The infrared, ultraviolet, and nuclear magnetic resonance spectra were consistent with those shown by an analytical standard of fenthion. The technical-grade fenthion as described above will be referred to as fenthion in this report.

The bulk chemical was stored at $4^{o}C$.

B. Dietary Preparation

All diets were formulated weekly using Wayne® Lab Blox meal (Allied Mills, Inc., Chicago, Ill.) to which was added the

required amount of fenthion. The test compound was first dissolved in a small amount of acetone (Mallinckrodt Inc., St. Louis, Mo.) which was then added to the feed. Corn oil (LouAna®, Opelousas Refinery, Opelousas, La.) was also added to the feed at 2% of the final feed weight, primarily as a dust suppressant. The diets were mixed mechanically for not less than 25 minutes to assure homogeneity and to allow for evaporation of the acetone. Diets for the control groups of animals also contained corn oil equal to 2% of the final weight of feed.

The stability of fenthion in feed was tested by determining the concentration of the compound in formulated diets at intervals over a 7-day period. Diets containing 10 or 320 ppm fenthion showed no significant change in fenthion concentration on standing at ambient temperatures for this period. Formulated diets were, therefore, stored at room temperature until used, but not longer than 1 week.

As a quality control check on the accuracy of preparation of the diets, the concentration of fenthion was determined in randomly selected batches of formulated diets at 8-week intervals during the chronic studies. The results of these analyses are reported in Appendix G. At each dietary concentration, the mean value

obtained was within 0.9% of the theoretical, and the coefficient of variation was 6.74% or less.

C. Animals

F344 rats and B6C3F1 mice of each sex, obtained through contracts of the Division of Cancer Treatment, NCI, were used in these bioassays. The rats and mice were bred at and supplied by the NCI Frederick Cancer Research Center, Frederick, Maryland. On arrival at the laboratory, all animals were quarantined for 16 days, then assigned to dosed or control groups. The rats were 6 weeks of age and the mice were 7 weeks of age when placed on study.

D. Animal Maintenance

All animals were housed in rooms in which the temperature ranged from 22 to 24°C, and the relative humidity from 40 to 70%. The air in each room was filtered through fiberglass filters (Air Maze Incom International, Cleveland, Ohio), and room air was changed 10 to 12 times per hour. Fluorescent lighting provided illumination 10 hours per day. Food and tap water were available

ad libitum. Fresh feed was provided daily, and excess remaining feed was discarded.

The rats were housed individually in hanging galvanized steel mesh cages (Hoeltge, Inc., Cincinnati, Ohio), and the mice were housed in polypropylene cages (Lab Products, Inc., Garfield, N.J.) containing five females per cage or two or three males per cage. Mouse cages were covered with polyester filter bonnets (Lab Products, Inc.). The racks and cages for the rats were sanitized every 2 weeks. The mouse cages were sanitized each week. These cages and racks were washed in an industrial washer at 82°C with Acclaim® detergent (Economics Laboratory, Inc., St. Paul, Minn.) and then rinsed. Absorbent Kimpak® cage liners (Kimberly Clark Corp., Neenah, Wis.) were placed under the rat cages and were changed three times per week. Absorb-dri® hardwood chip bedding (Lab Products, Inc.), used in the mouse cages, was provided two times per week for males and and three times per week for females. Filter bonnets were sanitized each week. Feeder jars and water bottles were changed and sanitized three times per week. Sipper tubes and stoppers were sanitized two times per week.

The filter bonnets, feed jars, water bottles, sipper tubes, and stoppers were washed in a Vulcan Autosan washer (Louisville, Ky.).

Cage racks for each species were rotated to a new position in the room once per week; at the same time, each cage was moved to a different row within the same column of a rack. Rats and mice receiving fenthion were housed in separate rooms. Control and dosed rats were housed on the same rack, whereas cages for control and dosed mice were placed on separate racks in the same room.

E. Subchronic Studies

Subchronic feeding studies were conducted to estimate the maximum tolerated doses (MTD's) of fenthion, on the basis of which two concentrations (hereinafter referred to in this report as "low" and "high" doses) were determined for administration in the chronic studies. Groups of 10 males and 10 females of each species were administered fenthion at one of several doses, and groups of 10 control animals of each species and sex were administered basal diet only. The period of administration of the test chemical was 13 weeks, after which the animals were killed and necropsied. Animals were weighed each week. Table 1 shows the number of animals that survived during the course of administration and the week on study when the last death occurred. The table also shows the mean body weights of the dosed animals at week 13, expressed as percentages of mean body weights of

Table 1. Fenthion Subchronic Feeding Studies in Rats and Mice

	Male			Female		
Dose (ppm)	Survival (a)	Week on Study when Last Animal Died	Mean Weight at Week 13 as % of Control	Survival (a)	Week on Study when Last Animal Died	Mean Weight at Week 13 as % of Control
Rats						
5	10/10		99	10/10		100
10	10/10		101	10/10		99
20	10/10		102	10/10		103
40	10/10		102	10/10		104
80	10/10		98	10/10		103
160	10/10		93	10/10		96
320	10/10		79	9/10	10	80
Mice						
5	10/10		93	10/10		104
10	10/10		96	10/10		104
20	10/10		107	10/10		100
40	10/10		107	10/10		104
80(b)	10/10		104	10/10		100
160	10/10		96	10/10		104
320	10/10		107	10/10		100

(a) Number surviving/number in group.

(b) One animal (sex not recorded) showed enlargement of lymph nodes, spleen, and liver. Histopathologic examination indicated a reticulum-cell sarcoma, which appeared to be a coincidental lesion.

controls. Histopathologic findings are shown as footnotes to the table.

In previous bioassays of organophosphorus chemicals at this laboratory, chronic doses based on subchronic tests were toxic. Thus, doses for the chronic studies in both rats and mice were set at relatively low concentrations (10 and 20 ppm).

F. Chronic Studies

The test groups, doses administered, and durations of the chronic feeding studies are shown in tables 2 and 3.

G. Clinical and Pathologic Examinations

All animals were observed twice daily. Clinical examination for signs of toxicity and palpation for masses were performed each month, and the animals were weighed every 2 weeks. Moribund animals and animals that survived to the end of the bioassay were killed using pentobarbitol and necropsied. Necropsies were also performed on all animals found dead, unless precluded by autolysis or severe cannibalization.

Table 2. Fenthion Chronic Feeding Studies in Rats

Sex and Test Group	Initial No. of Animals (a)	Fenthion Doses (b) (ppm)	Time on Study	
			Dosed (weeks)	Observed (weeks)
Male				
Matched-Control	25	0		105
Low-Dose	50	10	103	1-2
High-Dose	50	20	103	1-2
Female				
Matched-Control	25	0		104-105
Low-Dose	50	10	103	2
High-Dose	50	20	103	2

(a) Rats were 6 weeks of age when placed on study.

(b) Test and control diets were available *ad libitum*.

Table 3. Fenthion Chronic Feeding Studies in Mice

Sex and Test Group	Initial No. of Animals (a)	Fenthion Doses (b) (ppm)	Time on Study	
			Dosed (weeks)	Observed (weeks)
Male				
Matched-Control	25	0		103-104
Low-Dose	50	10	103	0-1
High-Dose	50	20	103	0-1
Female				
Matched-Control	25	0		103-104
Low-Dose	50	10	103	0-1
High-Dose	50	20	103	0-1

(a) Mice were 7 weeks of age when placed on study.

(b) Test and control diets were available *ad libitum*.

The pathologic evaluation consisted of gross and microscopic examination of major tissues, major organs, and all gross lesions. The following tissues were examined microscopically: skin, lungs and bronchi, trachea, bone and bone marrow, spleen, lymph nodes, heart, salivary gland, liver, gallbladder (mice), pancreas, stomach, small intestine, large intestine, kidney, urinary bladder, pituitary, adrenal, thyroid, parathyroid, mammary gland, prostate or uterus, testis or ovary, and brain. Occasionally, additional tissues were also examined microscopically. The different tissues were preserved in 10% buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Special staining techniques were utilized when indicated for more definitive diagnosis. Blood smears of all animals were routinely prepared.

A few tissues from some animals were not examined, particularly from those animals that may have died early, been missing, or been in advanced states of cannibalization or autolysis. Thus, the number of animals from which particular organs or tissues were examined microscopically varies and does not necessarily represent the number of animals that were placed on study in each group.

H. Data Recording and Statistical Analyses

Pertinent data on this experiment have been recorded in an automatic data processing system, the Carcinogenesis Bioassay Data System (Linhart et al., 1974). The data elements include descriptive information on the chemicals, animals, experimental design, clinical observations, survival, body weight, and individual pathologic results, as recommended by the International Union Against Cancer (Berenblum, 1969). Data tables were generated for verification of data transcription and for statistical review.

These data were analyzed using the appropriate statistical techniques described in this section. Those analyses of the experimental results that bear on the possibility of carcinogenicity are discussed in the statistical narrative sections.

Probabilities of survival were estimated by the product-limit procedure of Kaplan and Meier (1958) and are presented in this report in the form of graphs. Animals were statistically censored as of the time that they died of other than natural causes or were found to be missing; animals dying from natural causes were not statistically censored. Statistical analyses for

a possible dose-related effect on survival used the method of Cox (1972) for testing two groups for equality and Tarone's (1975) extensions of Cox's methods for testing for a dose-related trend. One-tailed P values have been reported for all tests except the departure from linearity test, which is only reported when its two-tailed P value is less than 0.05.

The incidence of neoplastic or nonneoplastic lesions has been given as the ratio of the number of animals bearing such lesions at a specific anatomic site (numerator) to the number of animals in which that site is examined (denominator). In most instances, the denominators included only those animals for which that site was examined histologically. However, when macroscopic examination was required to detect lesions prior to histologic sampling (e.g., skin or mammary tumors), or when lesions could have appeared at multiple sites (e.g., lymphomas), the denominators consist of the numbers of animals necropsied.

The purpose of the statistical analyses of tumor incidence is to determine whether animals receiving the test chemical developed a significantly higher proportion of tumors than did the control animals. As a part of these analyses, the one-tailed Fisher exact test (Cox, 1970) was used to compare the tumor incidence of a control group with that of a group of dosed animals at each

dose level. When results for a number of dosed groups (k) are compared simultaneously with those for a control group, a correction to ensure an overall significance level of 0.05 may be made. The Bonferroni inequality (Miller, 1966) requires that the P value for any comparison be less than or equal to 0.05/k. In cases where this correction was used, it is discussed in the narrative section. It is not, however, presented in the tables, where the Fisher exact P values are shown.

The Cochran-Armitage test for linear trend in proportions, with continuity correction (Armitage, 1971), was also used. Under the assumption of a linear trend, this test determines if the slope of the dose-response curve is different from zero at the one-tailed 0.05 level of significance. Unless otherwise noted, the direction of the significant trend is a positive dose relationship. This method also provides a two-tailed test of departure from linear trend.

A time-adjusted analysis was applied when numerous early deaths resulted from causes that were not associated with the formation of tumors. In this analysis, deaths that occurred before the first tumor was observed were excluded by basing the statistical tests on animals that survived at least 52 weeks, unless a tumor was found at the anatomic site of interest before week 52. When

such an early tumor was found, comparisons were based exclusively on animals that survived at least as long as the animal in which the first tumor was found. Once this reduced set of data was obtained, the standard procedures for analyses of the incidence of tumors (Fisher exact tests, Cochran-Armitage tests, etc.) were followed.

When appropriate, life-table methods were used to analyze the incidence of tumors. Curves of the proportions surviving without an observed tumor were computed as in Saffiotti et al. (1972). The week during which an animal died naturally or was sacrificed was entered as the time point of tumor observation. Cox's methods of comparing these curves were used for two groups; Tarone's extension to testing for linear trend was used for three groups. The statistical tests for the incidence of tumors which used life-table methods were one-tailed and, unless otherwise noted, in the direction of a positive dose relationship. Significant departures from linearity (P less than 0.05, two-tailed test) were also noted.

The approximate 95 percent confidence interval for the relative risk of each dosed group compared to its control was calculated from the exact interval on the odds ratio (Gart, 1971). The relative risk is defined as p_t/p_c where p_t is the true

binomial probability of the incidence of a specific type of tumor in a dosed group of animals and p_c is the true probability of the spontaneous incidence of the same type of tumor in a control group. The hypothesis of equality between the true proportion of a specific tumor in a dosed group and the proportion in a control group corresponds to a relative risk of unity. Values in excess of unity represent the condition of a larger proportion in the dosed group than in the control.

The lower and upper limits of the confidence interval of the relative risk have been included in the tables of statistical analyses. The interpretation of the limits is that in approximately 95% of a large number of identical experiments, the true ratio of the risk in a dosed group of animals to that in a control group would be within the interval calculated from the experiment. When the lower limit of the confidence interval is greater than one, it can be inferred that a statistically significant result (P less than 0.025 one-tailed test when the control incidence is not zero, P less than 0.050 when the control incidence is zero) has occurred. When the lower limit is less than unity, but the upper limit is greater than unity, the lower limit indicates the absence of a significant result while the upper limit indicates that there is a theoretical possibility of

the induction of tumors by the test chemical, which could not be detected under the conditions of this test.

III. RESULTS - RATS

A. Body Weights and Clinical Signs (Rats)

Mean body weights of the male and female rats did not differ appreciably from those of their respective controls at any time during the bioassay (figure 1).

During the first year on study, the dosed animals were generally comparable to the controls in appearance and behavior. Clinical signs were noted at a low incidence in both dosed and control groups. These signs included loss of weight, rough hair coats, and exudate from eyes; one low-dose female appeared to have abdominal distention and had vaginal bleeding. During the second year on study, clinical signs increased in frequency in both dosed and control groups. These signs included rough and discolored hair coats, loss of weight, pale mucous membranes, poor food consumption, loose stools, discolored (dark) urine, abdominal distention, vaginal bleeding, and tachypnea.

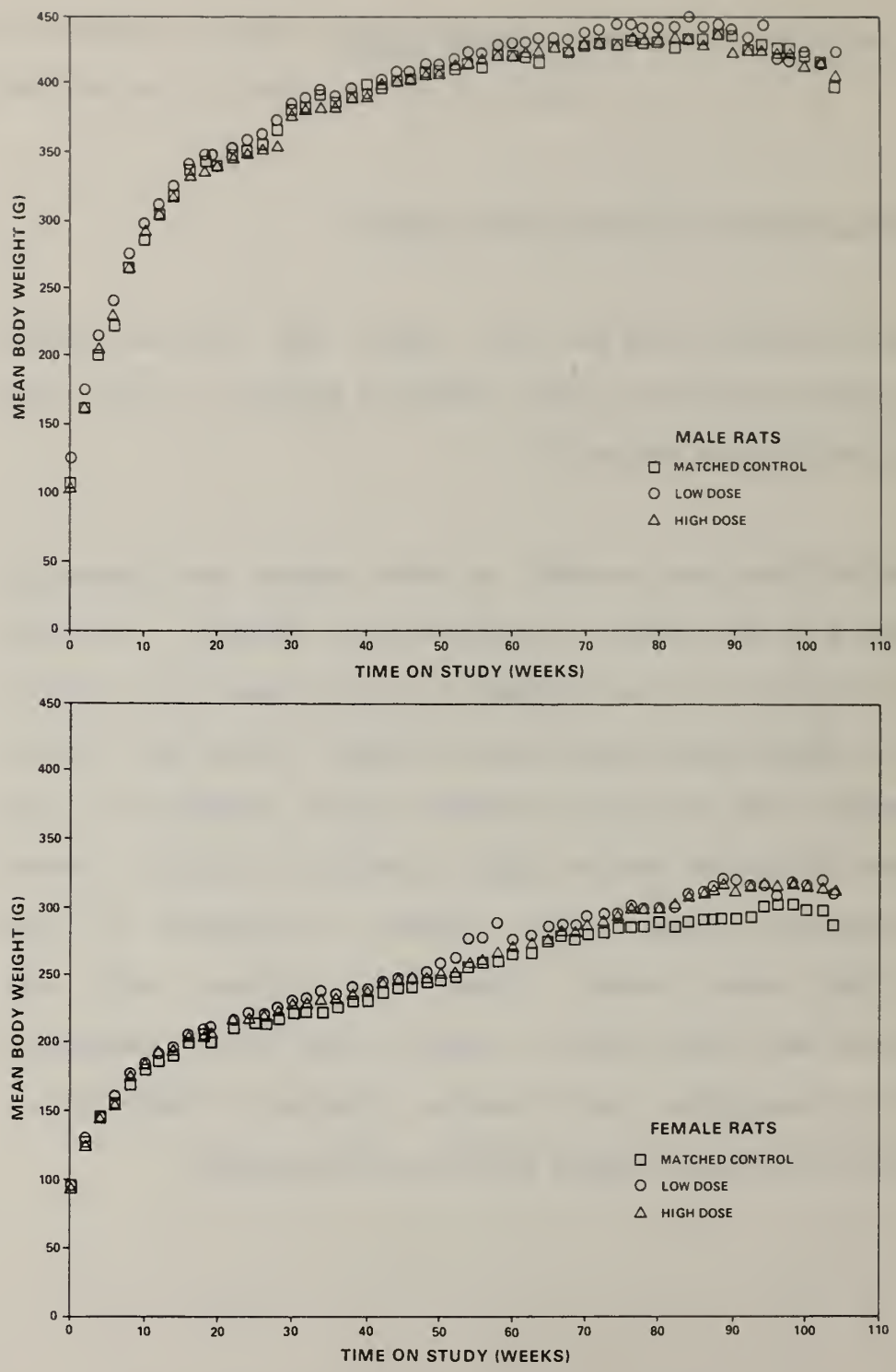


Figure 1. Growth Curves for Rats Administered Fenthion in the Diet

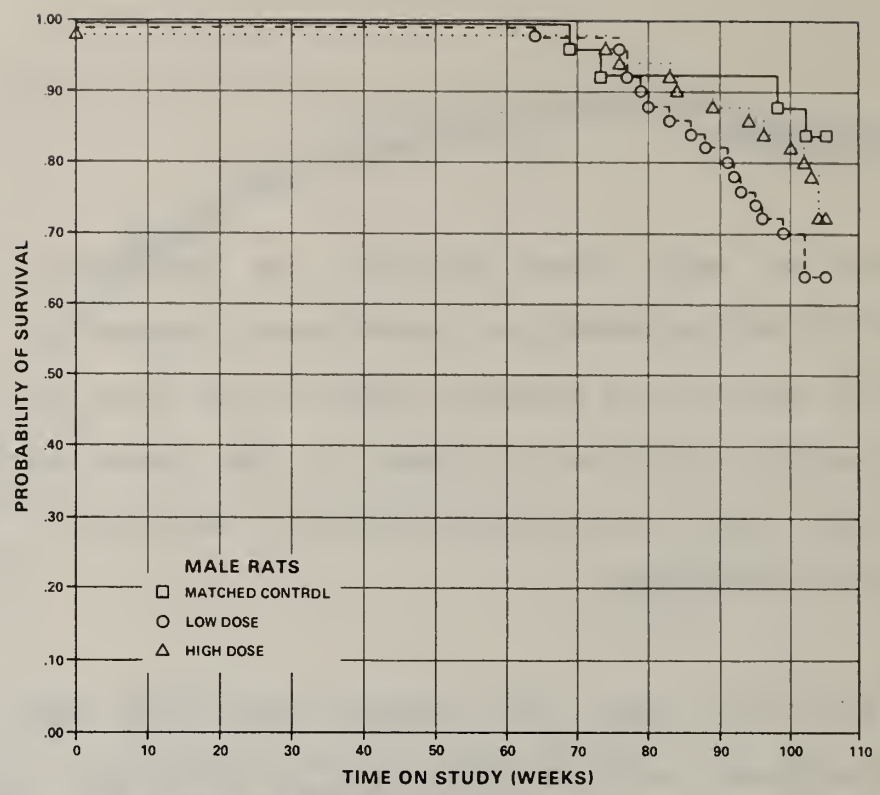
B. Survival (Rats)

The Kaplan and Meier curves estimating the probabilities of survival for male and female rats administered fenthion in the diet at the doses of this bioassay, together with those of the matched controls, are shown in figure 2. The result of the Tarone test for positive dose-related trend in mortality is not significant in either sex.

In male rats, 40/50 (80%) of the high-dose group, 32/50 (64%) of the low-dose group, and 21/25 (84%) of the matched-control group were alive at week 103. In females, 32/50 (64%) of the high-dose group, 38/50 (76%) of the low-dose group, and 16/25 (64%) of the matched-control group were alive at week 103. Sufficient numbers of rats of each sex were at risk for the development of late-appearing tumors.

C. Pathology (Rats)

Histopathologic findings on neoplasms in rats are summarized in Appendix A, tables A1 and A2; findings on nonneoplastic lesions are summarized in Appendix C, tables C1 and C2.



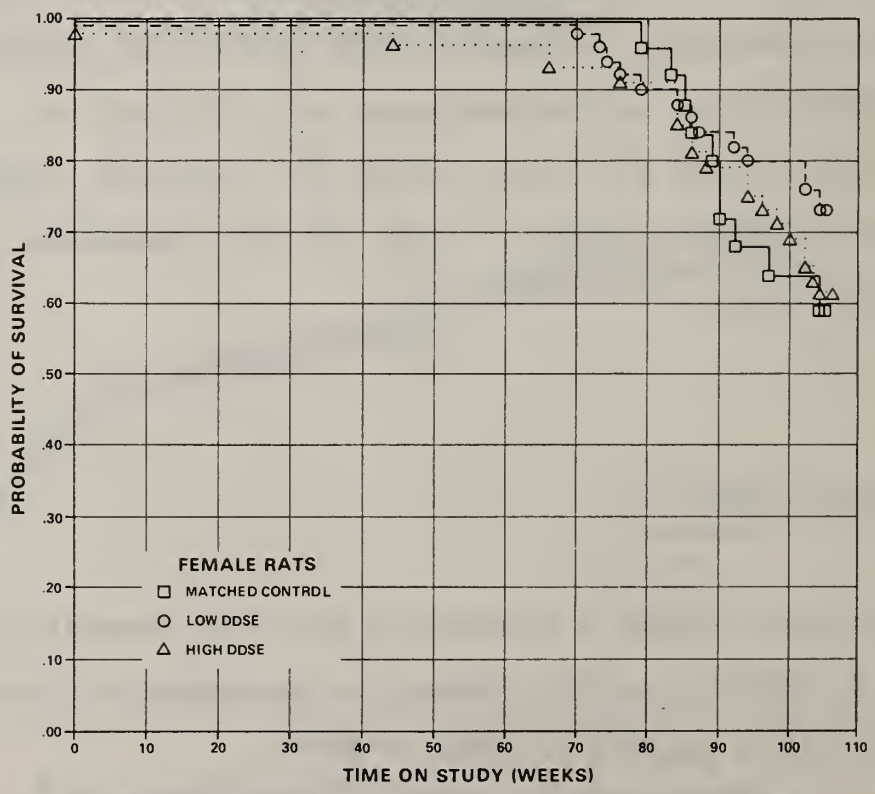


Figure 2. Survival Curves for Rats Administered Fenthion in the Diet

Neoplasms occurred with a comparable incidence among dosed and control animals. An exception to this was seen in C-cell adenomas of the thyroid, where there was an increased incidence of tumors in the low-dose female rats (12/48) as compared with the high-dose (4/46) and control (2/22) groups which were similar.

A variety of common nonneoplastic lesions were encountered. The numbers of specific lesions were small, however, and they appeared to be unrelated to the administration of fenthion.

Chronic inflammation of the submaxillary salivary gland occurred with a rather high incidence in dosed and control groups of both sexes. Viral inclusion bodies were not clearly evident. The inflammatory reaction was limited to the submaxillary gland and did not extend to the closely adjoining sublingual gland. These lesions were not considered to be compound related.

Based on the histopathologic examination, fenthion was not carcinogenic in F344 rats under the conditions of this bioassay.

D. Statistical Analyses of Results (Rats)

Tables E1 and E2 in Appendix E contain the statistical analyses

of the incidences of those primary tumors that occurred in at least two animals of one group and at an incidence of at least 5% in one or more than one group.

In male rats, the result of the Cochran-Armitage test for dose-related trend in the incidence of interstitial-cell tumors of the testis is significant (P = 0.028), but the results of the Fisher exact test are not significant. Historical records for this strain of rats indicate spontaneous incidences of tumors at rates between 75 and 100%. A significant dose-related trend (P = 0.036) in the negative direction is observed in the incidence of fibromas of the integumentary system in male rats and in the incidence of adenocarcinomas of the mammary gland in female rats, in which the incidence in the control group exceeds the incidences in the dosed groups.

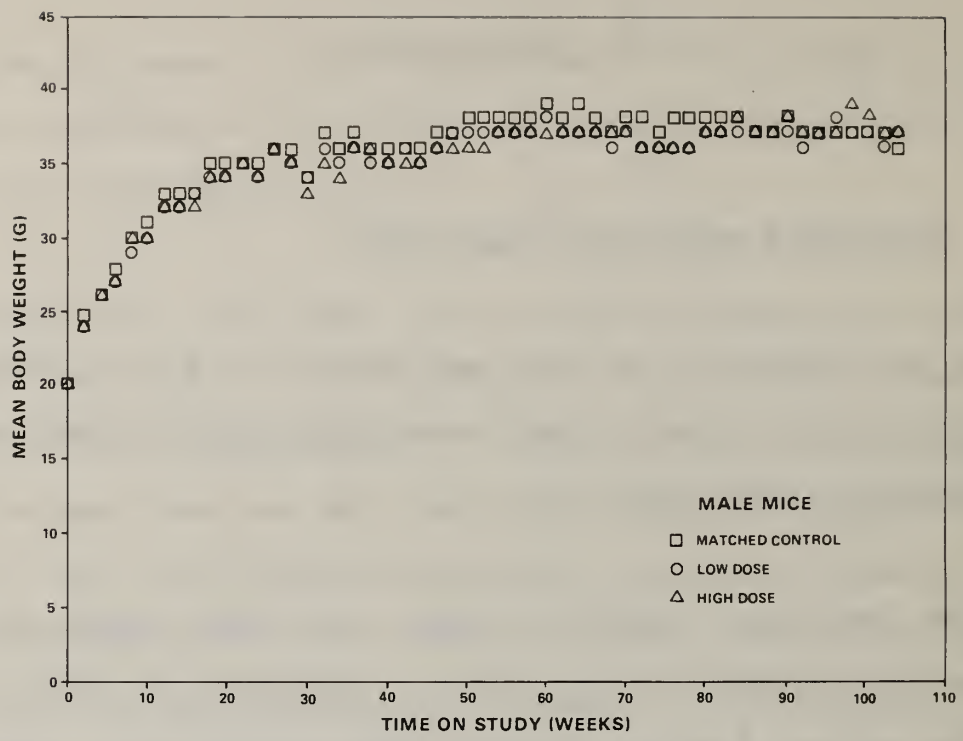
In each of the 95% confidence intervals of relative risk, shown in the tables, the value of one is included; this indicates the absence of significant positive results. It should also be noted that each of the intervals has an upper limit greater than one, indicating the theoretical possibility of the induction of tumors by fenthion, which could not be detected under the conditions of this test.

IV. RESULTS - MICE

A. Body Weights and Clinical Signs (Mice)

Mean body weights of the male and female mice did not differ appreciably from those of their respective controls at any time during the bioassay (figure 3).

During the first 4 months on study, the dosed animals were generally comparable to the controls in appearance and behavior. During the next 8 months, clinical signs were noted at a fairly low incidence. These signs included alopecia, loss of weight, and rough and discolored hair coats. Fighting was observed among the male mice, but predominantly in the dosed groups. This increased aggression resulted in traumatic conditions ranging from genital mutilation to death and cannibalism, which persisted until termination of the study. During the second year on study, the incidence of clinical signs increased in the dosed animals. These signs included pale mucous membranes, alopecia, tachypnea, and abdominal distention. Some animals in all groups appeared hyporeactive. A majority of the high-dose females exhibited a yellow discoloration of the hair coat during the last 5 months.



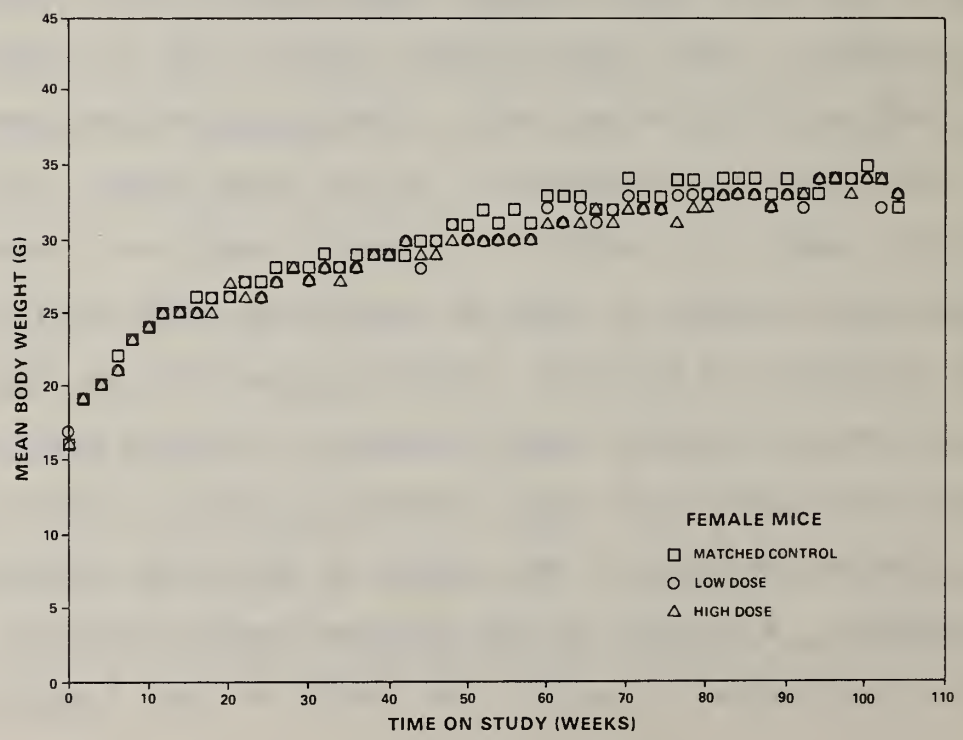


Figure 3. Growth Curves for Mice Administered Fenthion in the Diet

B. Survival (Mice)

The Kaplan and Meier curves estimating the probabilities of survival for male and female mice administered fenthion in the diet at the doses of this bioassay, together with those of the matched controls, are shown in figure 4. The result of the Tarone test for positive dose-related trend in mortality in the three groups is not significant in either sex. In male mice, an indicated departure (P = 0.005) from linear trend is observed, because the high-dose animals survived longer than the low-dose animals. The result of the Cox test comparing the survival of the low-dose group with that of the control group in male mice is significant (P = 0.015), but the results of this test are not significant when the survival of the high-dose group is compared with that of the control group.

In males, 38/50 (76%) of the high-dose group, 30/50 (60%) of the low-dose group, and 22/25 (88%) of the matched-control group were alive at week 103. In females, 41/50 (82%) of the high-dose group, 39/50 (78%) of the low-dose group, and 24/25 (96%) of the matched-control group were still alive at week 103. Sufficient numbers of mice of each sex were at risk for the development of late-appearing tumors.

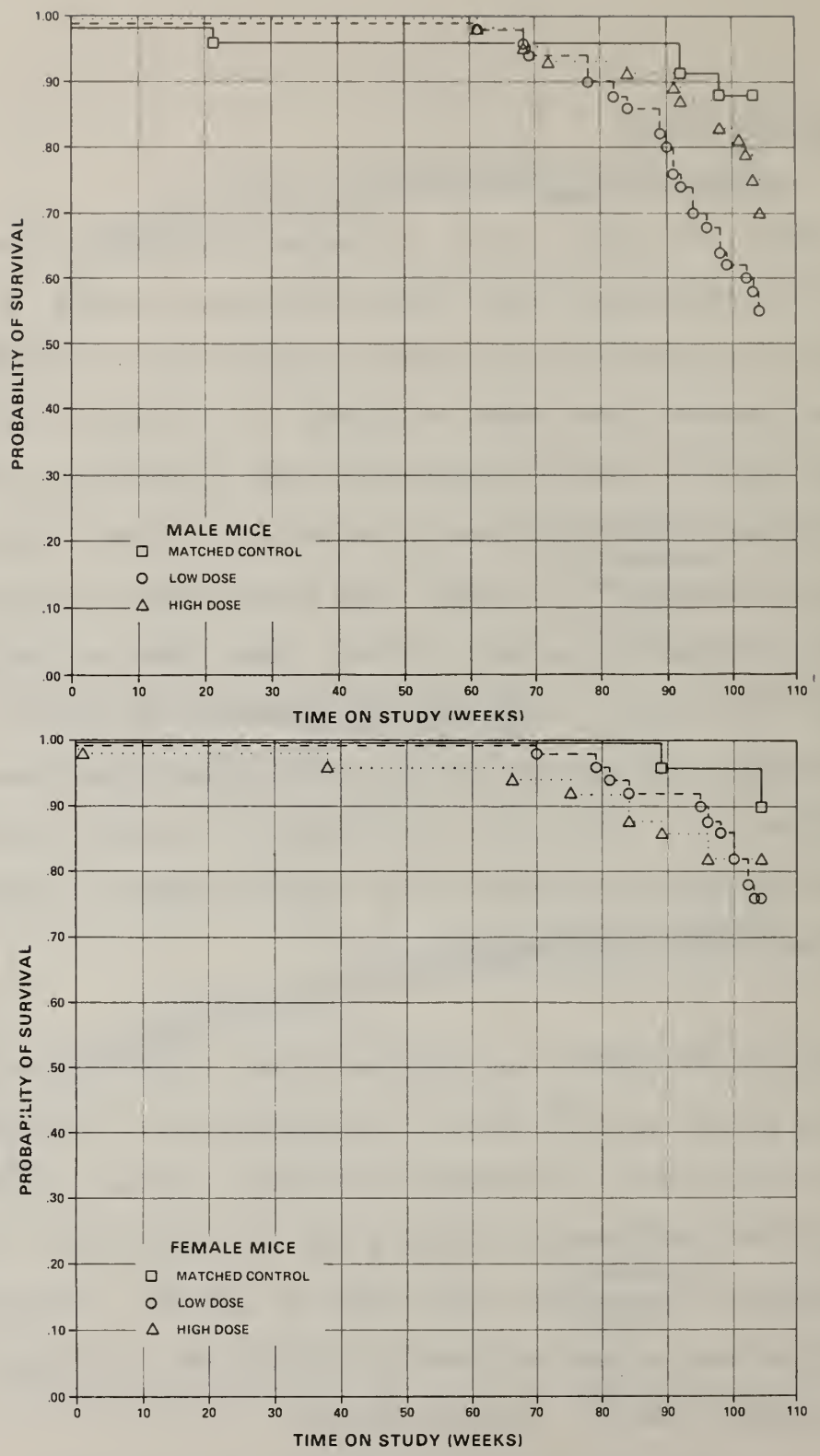


Figure 4. Survival Curves for Mice Administered Fenthion in the Diet

C. Pathology (Mice)

Histopathologic findings on neoplasms in mice are summarized in Appendix B, tables B1 and B2; findings on nonneoplastic lesions are summarized in Appendix D, tables D1 and D2.

A variety of neoplasms were represented among both dosed and control animals. The majority were not thought to be compound related. However, sarcomas of various types occurred with greater frequency in dosed male mice than in the controls, as follows:

	Control	Low Dose	High Dose
Skin and Subcutaneous Tissue	(25)	(49)	(48)
Sarcoma, NOS	0	0	2
Fibrosarcoma	0	4	4
Rhabdomyosarcoma	0	3	2

In female mice, the only such tumor was a fibrosarcoma observed in a low-dose animal. The integument was considered to be the primary site for all of the primary sarcomas, NOS, and fibrosarcomas. In the case of the rhabdomyosarcomas, the skeletal muscle within the subcutaneous tissue appeared to be the site of origin.

Histologically, differentiation was minimal to moderate among the various fibrosarcomas. Spindle-shaped fibroblastic elements were often arranged in a semi-whorled pattern with varying proportions of more primitive mesenchymal-type elements. Local invasiveness was readily apparent. In two cases, metastases occurred to the lungs and regional lymph node.

The rhabdomyosarcomas were composed of large, pleomorphic, relatively undifferentiated cells. Anaplasia was the rule rather than the exception. Strap-shaped and multinucleated elements were occasionally encountered. Rudimentary cross-striations were found in a few cells in sections stained with hematoxylin and eosin; special stains were not employed. Attempts to find unequivocal cross-striations in neoplastic cells were complicated by the fact that the few striations observed were poorly developed at best, and also by the necessity of differentiating striations within remnants of pre-existing skeletal muscle fibers undergoing myolysis in the midst of encroaching neoplastic elements. One of these neoplasms metastasized to the regional lymph node and invaded the pararenal tissue. Spontaneous rhabdomyosarcomas are considered rare in mice; thus, the incidence of 5% for dosed males may represent a compound-related effect.

The histopathologic examination provided evidence for the carcinogenicity of fenthion in male B6C3F1 mice, as there was a compound-related increase in sarcomas of the skin and subcutis.

D. Statistical Analyses of Results (Mice)

Tables F1 and F2 in Appendix F contain the statistical analyses of the incidences of those primary tumors that occurred in at least two animals of one group and at an incidence of at least 5% in one or more than one group.

In male mice, the results of the Cochran-Armitage test for dose-related trend in the incidence of animals with fibrosarcomas, sarcomas, or rhabdomyosarcomas of the integumentary system are significant (P = 0.043). The Fisher exact comparison of incidences between the low-dose and control groups shows a P value of 0.048 and between the high-dose and control groups a P value of 0.028. These two P values are above the 0.025 level required for significance when the Bonferroni inequality criterion is used for multiple comparisons. When the life-table method, using times of observations of the tumors, is applied, the result of the Tarone test is not significant. The historical records of control male B6C3F1 mice at this laboratory indicate

an incidence of animals with sarcomas or fibrosarcomas of the integumentary system of 7/435 (1.6%). The highest incidence of these fibrosarcomas or sarcomas in the 27 male historical-control groups at this laboratory was 4/25 (16%), but no rhabdomyosarcomas are observed in the historical records for the control male or female B6C3F1 mice. The incidences of animals with fibrosarcomas, sarcomas, NOS, and rhabdomyosarcomas in the low- and high-dose groups of this study are 7/49 (14%) and 8/48 (17%), respectively. These results suggest an association of these various types of sarcomas with the administration of fenthion.

In female mice, the results of the Cochran-Armitage test for positive dose-related trend in proportions and those of the Fisher exact test comparing the incidences in the control group with those in the dosed groups in the positive direction are not significant at any site. Significant results in the negative direction are observed in the incidence of papillary adenomas of the thyroid in female mice, where the incidence in the control group exceeds the incidences in the dosed groups. This negative significance may be because the control animals lived longer than the dosed animals.

V. DISCUSSION

Administration of fenthion to male and female F344 rats and female B6C3F1 mice resulted in no appreciable toxicity at the doses administered in this bioassay, since the mean body weights and the survivals of the dosed animals were generally unaffected. Among the male mice, 30/50 (60%) of the low-dose group and 38/50 (76%) of the high-dose group, compared with 22/25 (88%) of the controls were alive at week 103 and the survival of the low-dose group was significantly less than that of the control group. Thus, animals other than male mice may have been able to tolerate higher doses. However, fighting was observed among the male mice, particularly among the dosed animals, and it resulted in severe bite wounds and death. Sufficient numbers of animals in all groups of rats and mice were at risk for the development of late-appearing tumors.

In the male rats, interstitial-cell tumors of the testis occurred at incidences that were dose related ($P = 0.028$); however, the incidences of the tumors in the individual dosed groups were not significantly higher than the incidence in the control group (controls 18/24, low-dose 37/50, high-dose 45/49). Also, this tumor is known to occur spontaneously at high incidences (70 to

100%) in F344 male rats. Thus, the occurrence of interstitial-cell tumors of the testis in the dosed males of the present bioassay cannot clearly be related to administration of fenthion.

In the female rats and also in the female mice, no tumors occurred at incidences that were significantly higher in dosed groups than in control groups.

In the male mice, sarcomas, fibrosarcomas, or rhabdomyosarcomas of the integumentary system occurred at incidences that were dose related (P = 0.043). In direct comparisons of the incidences of these tumors in the dosed groups with the incidence in the control group, the P values of 0.048 and 0.028 for the low- and high-dose groups, respectively, did not meet the Bonferroni criterion of P = 0.025 for significance when multiple comparisons are made (controls 0/25; low-dose 7/49, or 14%; high-dose 8/48, or 17%). However, the incidence of sarcomas and fibrosarcomas in historical-control male B6C3F1 mice used in bioassays of all chemicals tested at this same laboratory was only 7/435 (1.6%), and no rhabdomyosarcomas occurred in the historical-control male mice. Thus, the increased incidence of sarcomas, fibrosarcomas, or rhabdomyosarcomas of the integumentary system in the dosed

male mice of the present bioassay was associated with the administration of the test chemical.

In a previously published study, when rats (strain not specified) were administered diets containing 0, 2, 3, 5, 25, and 100 ppm fenthion for 1 year, the dosed animals had no significant change in general appearance, growth rate, food consumption, and gross or microscopic appearance of tissues (Doull et al., 1963).

It is concluded that under the conditions of this bioassay, fenthion was not carcinogenic for male or female F344 rats or for female B6C3F1 mice. The increased incidence of sarcomas, fibrosarcomas, and especially rhabdomyosarcomas of the integumentary system in the male B6C3F1 mice suggested that the test chemical was carcinogenic in these animals.

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS ADMINISTERED FENTHION IN THE DIET

TABLE A1.
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS ADMINISTERED FENTHION IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	25	50	50
ANIMALS NECROPSIED	25	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	25	50	49
INTEGUMENTARY SYSTEM			
*SKIN	(25)	(50)	(49)
PAPILLOMA, NOS		1 (2%)	
SQUAMOUS CELL CARCINOMA	1 (4%)		
FIBROMA	2 (8%)		
RESPIRATORY SYSTEM			
#LUNG	(25)	(49)	(49)
ALVEOLAR/BRONCHIOLAR ADENOMA			1 (2%)
OSTEOSARCOMA, METASTATIC			1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(25)	(50)	(49)
LEUKEMIA,NOS	2 (8%)	1 (2%)	
INDIFFERENTIATED LEUKEMIA		1 (2%)	
LYMPHOCYTIC LEUKEMIA		2 (4%)	
GRANULOCYTIC LEUKEMIA		1 (2%)	
MONOCYTIC LEUKEMIA	4 (16%)	4 (8%)	8 (16%)
#SPLEEN	(25)	(47)	(49)
HEMANGIOMA		1 (2%)	
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(25)	(49)	(49)
NEOPLASTIC NODULE		1 (2%)	1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
HEPATOCELLULAR CARCINOMA		1 (2%)	
HEMANGIOMA		1 (2%)	
#PANCREAS	(24)	(47)	(49)
ACINAR-CELL ADENOMA			1 (2%)
#JEJUNUM	(24)	(48)	(48)
ADENOCARCINOMA, NOS	1 (4%)		
#CECUM	(24)	(47)	(47)
ADENOMATOUS POLYP, NOS		1 (2%)	
URINARY SYSTEM			
#KIDNEY	(25)	(49)	(48)
OSTEOSARCOMA, METASTATIC			1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(25)	(47)	(44)
CARCINOMA,NOS		4 (9%)	
ADENOMA, NOS			1 (2%)
CHROMOPHOBE ADENOMA	9 (36%)	12 (26%)	9 (20%)
#ADRENAL	(25)	(49)	(49)
CARCINOMA,NOS		1 (2%)	
PHEOCHROMOCYTOMA			1 (2%)
#THYROID	(23)	(44)	(27)
FOLLICULAR-CELL CARCINOMA		2 (5%)	
C-CELL ADENOMA	2 (9%)	5 (11%)	3 (11%)
#PANCREATIC ISLETS	(24)	(47)	(49)
ISLET-CELL ADENOMA	2 (8%)	1 (2%)	2 (4%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(25)	(50)	(49)
FIBROMA	1 (4%)	1 (2%)	
#TESTIS	(24)	(50)	(49)
INTERSTITIAL-CELL TUMOR	18 (75%)	37 (74%)	45 (92%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
NERVOUS SYSTEM			
*BRAIN	(25)	(49)	(49)
SQUAMOUS CELL CARCINOMA, METASTA			1 (2%)
SPECIAL SENSE ORGANS			
*EAR	(25)	(50)	(49)
SQUAMOUS CELL CARCINOMA			1 (2%)
*EAR CANAL	(25)	(50)	(49)
PAPILLOMA, NOS			1 (2%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*PERITONEUM	(25)	(50)	(49)
MESOTHELIOMA, NOS			1 (2%)
MESOTHELIOMA, MALIGNANT			1 (2%)
*PLEURA	(25)	(50)	(49)
OSTEOSARCOMA			1 (2%)
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	25	50	50
NATURAL DEATH@	3	4	2
MORIBUND SACRIFICE	1	14	12
**SCHEDULED SACRIFICE	2	2	2
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	19	30	34
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
** Animals are in fact early terminal sacrifices, but appear as scheduled sacrifices due to system interpretation.

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	25	49	48
TOTAL PRIMARY TUMORS	42	78	77
TOTAL ANIMALS WITH BENIGN TUMORS	24	43	47
TOTAL BENIGN TUMORS	34	60	64
TOTAL ANIMALS WITH MALIGNANT TUMORS	7	16	11
TOTAL MALIGNANT TUMORS	8	17	11
TOTAL ANIMALS WITH SECONDARY TUMORS#			2
TOTAL SECONDARY TUMORS			3
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT		1	2
TOTAL UNCERTAIN TUMORS		1	2
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
\# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

TABLE A2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS ADMINISTERED FENTHION IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	25	50	50
ANIMALS NECROPSIED	25	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	25	50	49
INTEGUMENTARY SYSTEM			
*SKIN	(25)	(50)	(49)
PAPILLOMA, NOS		1 (2%)	
FIBROSARCOMA		1 (2%)	
RESPIRATORY SYSTEM			
NONE			
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(25)	(50)	(49)
LEUKEMIA,NOS	1 (4%)		1 (2%)
LYMPHOCYTIC LEUKEMIA		1 (2%)	1 (2%)
MONOCYTIC LEUKEMIA	2 (8%)	2 (4%)	9 (18%)
#SPLEEN	(25)	(49)	(49)
ADENOCARCINOMA, NOS, METASTATIC	1 (4%)		
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
*LIVER	(25)	(50)	(49)
NEOPLASTIC NODULE	1 (4%)		
#JEJUNUM	(24)	(49)	(49)
ADENOCARCINOMA, NOS	1 (4%)		
URINARY SYSTEM			
NONE			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#PITUITARY	(25)	(50)	(48)
CARCINOMA,NOS	1 (4%)		2 (4%)
ADENOMA, NOS			1 (2%)
CHROMOPHOBE ADENOMA	14 (56%)	20 (40%)	25 (52%)
#THYROID	(22)	(48)	(46)
FOLLICULAR-CELL ADENOMA			1 (2%)
C-CELL ADENOMA	2 (9%)	12 (25%)	4 (9%)
#PANCREATIC ISLETS	(25)	(49)	(49)
ISLET-CELL ADENOMA			1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(25)	(50)	(49)
ADENOCARCINOMA, NOS	2 (8%)		
PAPILLARY ADENOCARCINOMA			1 (2%)
FIBROMA			1 (2%)
LIPOMA		1 (2%)	
FIBROADENOMA	1 (4%)	6 (12%)	1 (2%)
#UTERUS	(25)	(49)	(46)
LEIOMYOSARCOMA		2 (4%)	1 (2%)
ENDOMETRIAL STROMAL POLYP	2 (8%)	11 (22%)	8 (17%)
#UTERUS/ENDOMETRIUM	(25)	(49)	(46)
ADENOCARCINOMA, NOS		1 (2%)	
#OVARY	(25)	(49)	(48)
ADENOCARCINOMA, NOS	1 (4%)		
GRANULOSA-CELL CARCINOMA		1 (2%)	
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*EYELID	(25)	(50)	(49)
FIBROUS HISTIOCYTOMA			1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
*EAR	(25)	(50)	(49)
FIBROMA	1 (4%)		
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*PERITONEAL CAVITY	(25)	(50)	(49)
ADENOCARCINOMA, NOS, INVASIVE	1 (4%)		
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(25)	(50)	(49)
FIBROUS HISTIOCYTOMA, MALIGNANT			1 (2%)
MESOTHELIOMA, MALIGNANT			1 (2%)
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	25	50	50
NATURAL DEATH@	1	1	2
MORIBUND SACRIFICE	9	12	17
**SCHEDULED SACRIFICE	2	2	2
ACCIDENTALLY KILLED			1
TERMINAL SACRIFICE	13	35	28
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

** Animals are in fact early terminal sacrifices, but appear as scheduled sacrifices due to system interpretation.

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	18	44	39
TOTAL PRIMARY TUMORS	29	59	60
TOTAL ANIMALS WITH BENIGN TUMORS	16	39	33
TOTAL BENIGN TUMORS	20	51	43
TOTAL ANIMALS WITH MALIGNANT TUMORS	6	8	16
TOTAL MALIGNANT TUMORS	8	8	17
TOTAL ANIMALS WITH SECONDARY TUMORS#	2		
TOTAL SECONDARY TUMORS	2		
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	1		
TOTAL UNCERTAIN TUMORS	1		
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
\# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN

MICE ADMINISTERED FENTHION IN THE DIET

TABLE B1.
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE ADMINISTERED FENTHION IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	25	50	50
ANIMALS NECROPSIED	25	49	48
ANIMALS EXAMINED HISTOPATHOLOGICALLY	25	49	48
INTEGUMENTARY SYSTEM			
*SKIN	(25)	(49)	(48)
SARCOMA, NOS			1 (2%)
FIBROMA	1 (4%)		
FIBROSARCOMA		4 (8%)	1 (2%)
*SUBCUT TISSUE	(25)	(49)	(48)
SARCOMA, NOS			1 (2%)
FIBROMA			1 (2%)
FIBROSARCOMA			3 (6%)
RHABDOMYOSARCOMA		3 (6%)	2 (4%)
RESPIRATORY SYSTEM			
#LUNG	(25)	(48)	(48)
ALVEOLAR/BRONCHIOLAR ADENOMA	2 (8%)	5 (10%)	8 (17%)
RHABDOMYOSARCOMA, METASTATIC			1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(25)	(49)	(48)
MALIGNANT LYMPHOMA, NOS		1 (2%)	
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (4%)	3 (6%)	1 (2%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)
LYMPHOCYTIC LEUKEMIA		1 (2%)	
GRANULOCYTIC LEUKEMIA		1 (2%)	
*AXILLARY LYMPH NODE	(21)	(43)	(42)
FIBROSARCOMA, METASTATIC		1 (2%)	
#INGUINAL LYMPH NODE	(21)	(43)	(42)
RHABDOMYOSARCOMA, METASTATIC		1 (2%)	
CIRCULATORY SYSTEM			
NONE			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#LIVER	(25)	(49)	(48)
HEPATOCELLULAR ADENOMA		2 (4%)	4 (8%)
HEPATOCELLULAR CARCINOMA	6 (24%)	15 (31%)	13 (27%)
HEMANGIOSARCOMA		1 (2%)	
#STOMACH	(24)	(45)	(42)
ADENOMATOUS POLYP, NOS		1 (2%)	
#JEJUNUM	(24)	(43)	(40)
ADENOMATOUS POLYP, NOS	1 (4%)		
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY	(18)	(35)	(32)
CHROMOPHOBE ADENOMA		1 (3%)	
#ADRENAL	(21)	(48)	(46)
PHEOCHROMOCYTOMA		2 (4%)	1 (2%)
#THYROID	(23)	(39)	(35)
PAPILLARY ADENOMA	1 (4%)		
REPRODUCTIVE SYSTEM			
#TESTIS	(23)	(48)	(45)
SERTOLI-CELL TUMOR			1 (2%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*EYE/LACRIMAL GLAND	(25)	(49)	(48)
ADENOMA, NOS			1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*PERITONEUM	(25)	(49)	(48)
RHABDOMYOSARCOMA, METASTATIC		1 (2%)	
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	25	50	50
NATURAL DEATH@		2	4
MORIBUND SACRIFICE	3	20	10
**SCHEDULED SACRIFICE			1
ACCIDENTALLY KILLED			1
TERMINAL SACRIFICE	22	28	34
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

**Animal is in fact an early terminal sacrifice, but appears as a scheduled sacrifice due to system interpretation.

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	10	35	26
TOTAL PRIMARY TUMORS	12	40	39
TOTAL ANIMALS WITH BENIGN TUMORS	4	10	16
TOTAL BENIGN TUMORS	5	11	16
TOTAL ANIMALS WITH MALIGNANT TUMORS	7	28	20
TOTAL MALIGNANT TUMORS	7	29	23
TOTAL ANIMALS WITH SECONDARY TUMORS#		2	1
TOTAL SECONDARY TUMORS		3	1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
\# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

TABLE B2.
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE ADMINISTERED FENTHION IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	25	50	50
ANIMALS NECROPSIED	24	47	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	24	47	50
INTEGUMENTARY SYSTEM			
*SKIN	(24)	(47)	(50)
FIBROSARCOMA		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(24)	(46)	(50)
ALVEOLAR/BRONCHIOLAR ADENOMA	2 (8%)	3 (7%)	3 (6%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (4%)		
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(24)	(47)	(50)
MALIGNANT LYMPHOMA, NOS		1 (2%)	
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	4 (17%)	6 (13%)	12 (24%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		2 (4%)	
#SPLEEN	(24)	(45)	(48)
HEMANGIOSARCOMA, METASTATIC		1 (2%)	
MALIG.LYMPHOMA, UNDIFFER-TYPE		1 (2%)	
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (4%)		
#MANDIBULAR L. NODE	(21)	(46)	(43)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (5%)		
#LIVER	(24)	(47)	(50)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		2 (4%)	
#KIDNEY	(23)	(47)	(48)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE			1 (2%)
CIRCULATORY SYSTEM			
*BLOOD VESSEL	(24)	(47)	(50)
HEMANGIOSARCOMA	1 (4%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#LIVER	(24)	(47)	(50)
HEPATOCELLULAR ADENOMA			1 (2%)
HEPATOCELLULAR CARCINOMA	2 (8%)	4 (9%)	1 (2%)
HEMANGIOSARCOMA		2 (4%)	
#STOMACH	(24)	(44)	(41)
ADENOMATOUS POLYP, NOS			1 (2%)
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY	(21)	(37)	(42)
ADENOMA, NOS		1 (3%)	3 (7%)
CHROMOPHOBE ADENOMA		1 (3%)	
ACIDOPHIL ADENOMA		1 (3%)	1 (2%)
#ADRENAL	(23)	(45)	(46)
PHEOCHROMOCYTOMA			1 (2%)
#THYROID	(21)	(42)	(40)
PAPILLARY ADENOMA	3 (14%)		
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(24)	(47)	(50)
ADENOCARCINOMA, NOS		2 (4%)	
FIBROADENOMA	1 (4%)	1 (2%)	2 (4%)
#UTERUS	(19)	(45)	(40)
FIBROMA			1 (3%)
HEMANGIOMA	1 (5%)		
#OVARY	(24)	(40)	(43)
GRANULOSA-CELL TUMOR			1 (2%)
TERATOMA, BENIGN			1 (2%)
NERVOUS SYSTEM			
NONE			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
SPECIAL SENSE ORGANS			
*EYE/LACRIMAL GLAND	(24)	(47)	(50)
ADENOMA, NOS			2 (4%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(24)	(47)	(50)
SARCOMA, NOS			1 (2%)
FIBROSARCOMA	1 (4%)		
RHABDOMYOSARCOMA		1 (2%)	
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	25	50	50
NATURAL DEATH@	1	4	3
MORIBUND SACRIFICE	1	8	6
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	23	38	41
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	12	22	24
TOTAL PRIMARY TUMORS	18	29	32
TOTAL ANIMALS WITH BENIGN TUMORS	6	6	14
TOTAL BENIGN TUMORS	7	7	16
TOTAL ANIMALS WITH MALIGNANT TUMORS	9	20	15
TOTAL MALIGNANT TUMORS	11	22	15
TOTAL ANIMALS WITH SECONDARY TUMORS#		1	
TOTAL SECONDARY TUMORS		1	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			1
TOTAL UNCERTAIN TUMORS			1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
\# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS ADMINISTERED FENTHION IN THE DIET

TABLE C1.
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS ADMINISTERED FENTHION IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	25	50	50
ANIMALS NECROPSIED	25	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	25	50	49
INTEGUMENTARY SYSTEM			
*SKIN	(25)	(50)	(49)
CYST, NOS	1 (4%)		
EPIDERMAL INCLUSION CYST			1 (2%)
MULTIPLE CYSTS	1 (4%)		
*SUBCUT TISSUE	(25)	(50)	(49)
EPIDERMAL INCLUSION CYST		1 (2%)	
NODULE		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(25)	(49)	(49)
HYPERPLASIA, ADENOMATOUS		1 (2%)	
HEMATOPOIETIC SYSTEM			
#SPLEEN	(25)	(47)	(49)
FIBROSIS, FOCAL		1 (2%)	1 (2%)
INFARCT, NOS			2 (4%)
#SPLENIC RED PULP	(25)	(47)	(49)
FIBROSIS			1 (2%)
#MESENTERIC L. NODE	(23)	(47)	(47)
CYST, NOS		1 (2%)	
INFLAMMATION, CHRONIC	1 (4%)		
CIRCULATORY SYSTEM			
#HEART/ATRIUM	(25)	(50)	(49)
THROMBUS, ORGANIZED		1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
#AURICULAR APPENDAGE	(25)	(50)	(49)
THROMBUS, ORGANIZED		1 (2%)	
#MYOCARDIUM	(25)	(50)	(49)
FIBROSIS, FOCAL		1 (2%)	
FIBROSIS, MULTIFOCAL			1 (2%)
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(24)	(48)	(48)
INFLAMMATION, CHRONIC	1 (4%)		1 (2%)
#SUBMAXILLARY GLAND	(24)	(48)	(48)
INFLAMMATION, ACUTE/CHRONIC		2 (4%)	
INFLAMMATION, CHRONIC	13 (54%)	13 (27%)	11 (23%)
#LIVER	(25)	(49)	(49)
METAMORPHOSIS FATTY		3 (6%)	
FOCAL CELLULAR CHANGE			1 (2%)
*BILE DUCT	(25)	(50)	(49)
INFLAMMATION, CHRONIC		1 (2%)	1 (2%)
HYPERPLASIA, NOS		2 (4%)	
HYPERPLASIA, FOCAL			1 (2%)
#PANCREAS	(24)	(47)	(49)
PERIARTERITIS			1 (2%)
#PANCREATIC ACINUS	(24)	(47)	(49)
ATROPHY, FOCAL		1 (2%)	
#STOMACH	(23)	(46)	(49)
ULCER, NOS		1 (2%)	
ULCER, ACUTE			1 (2%)
#GASTRIC SUBMUCOSA	(23)	(46)	(49)
EDEMA, NOS	2 (9%)		
#CECUM	(24)	(47)	(47)
POLYPOID HYPERPLASIA		1 (2%)	
URINARY SYSTEM			
#KIDNEY	(25)	(49)	(48)
INFLAMMATION, CHRONIC	18 (72%)	39 (80%)	40 (83%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
#URINARY BLADDER	(24)	(46)	(44)
INFLAMMATION, ACUTE		1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(25)	(47)	(44)
MULTIPLE CYSTS			1 (2%)
HEMORRHAGE			3 (7%)
HYPERPLASIA, FOCAL		1 (2%)	2 (5%)
#ADRENAL	(25)	(49)	(49)
DEGENERATION, CYSTIC			1 (2%)
#ADRENAL MEDULLA	(25)	(49)	(49)
HYPERPLASIA, NODULAR		3 (6%)	
#THYROID	(23)	(44)	(27)
HYPERPLASIA, C-CELL			1 (4%)
#THYROID FOLLICLE	(23)	(44)	(27)
HYPERPLASIA, CYSTIC		1 (2%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(25)	(50)	(49)
DYSPLASIA, NOS		1 (2%)	1 (2%)
#TESTIS	(24)	(50)	(49)
ATROPHY, NOS		3 (6%)	
NERVOUS SYSTEM			
#BRAIN	(25)	(49)	(49)
MALACIA		1 (2%)	
SPECIAL SENSE ORGANS			
*EAR	(25)	(50)	(49)
EPIDERMAL INCLUSION CYST		1 (2%)	
MUSCULOSKELETAL SYSTEM			
NONE			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
BODY CAVITIES			
*PERITONEUM	(25)	(50)	(49)
INFLAMMATION, CHRONIC FOCAL		1 (2%)	
NECROSIS, FAT			1 (2%)
*MESENTERY	(25)	(50)	(49)
NECROSIS, FAT		1 (2%)	
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED			1
AUTOLYSIS/NO NECROPSY			1

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2.
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS ADMINISTERED FENTHION IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	25	50	50
ANIMALS NECROPSIED	25	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	25	50	49
INTEGUMENTARY SYSTEM			
*SKIN	(25)	(50)	(49)
MULTIPLE CYSTS		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(25)	(50)	(49)
BRONCHOPNEUMONIA ACUTE SUPPURATI	1 (4%)		
HEMATOPOIETIC SYSTEM			
#SPLEEN	(25)	(49)	(49)
FIBROSIS, FOCAL	1 (4%)		
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(24)	(48)	(48)
INFLAMMATION, ACUTE/CHRONIC			2 (4%)
#SUBMAXILLARY GLAND	(24)	(48)	(48)
INFLAMMATION, CHRONIC	6 (25%)	16 (33%)	11 (23%)
#LIVER	(25)	(50)	(49)
INFLAMMATION, CHRONIC FOCAL		1 (2%)	
GRANULOMA, NOS	1 (4%)	2 (4%)	1 (2%)
DEGENERATION, GRANULAR	1 (4%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
NECROSIS, FOCAL		1 (2%)	
METAMORPHOSIS FATTY		1 (2%)	2 (4%)
#STOMACH	(23)	(49)	(49)
ULCER, ACUTE		2 (4%)	
URINARY SYSTEM			
#KIDNEY	(25)	(49)	(49)
HYDRONEPHROSIS		1 (2%)	
INFLAMMATION, CHRONIC	8 (32%)	22 (45%)	23 (47%)
CALCIFICATION, METASTATIC		1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(25)	(50)	(48)
CYST, NOS		4 (8%)	1 (2%)
HEMORRHAGE	5 (20%)	8 (16%)	5 (10%)
HYPERPLASIA, NOS		2 (4%)	
HYPERPLASIA, FOCAL		1 (2%)	1 (2%)
#THYROID	(22)	(48)	(46)
HYPERPLASIA, C-CELL			1 (2%)
HYPERPLASIA, FOLLICULAR-CELL		1 (2%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(25)	(50)	(49)
DYSPLASIA, NOS	8 (32%)	13 (26%)	14 (29%)
*MAMMARY LOBULE	(25)	(50)	(49)
HYPERPLASIA, NOS	2 (8%)	5 (10%)	1 (2%)
#UTERUS/ENDOMETRIUM	(25)	(49)	(46)
HYPERPLASIA, CYSTIC			1 (2%)
#OVARY	(25)	(49)	(48)
NECROSIS, FAT	1 (4%)	1 (2%)	1 (2%)
NERVOUS SYSTEM			
#BRAIN	(24)	(50)	(48)
HYDROCEPHALUS, NOS		1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
INFARCT, NOS			1 (2%)
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*ABDOMINAL CAVITY	(25)	(50)	(49)
NECROSIS, FAT			1 (2%)
*PERITONEUM	(25)	(50)	(49)
NECROSIS, FAT	1 (4%)		
*PERITONEAL CAVITY	(25)	(50)	(49)
NECROSIS, FAT			1 (2%)
*MESENTERY	(25)	(50)	(49)
NECROSIS, FAT	1 (4%)		
ALL OTHER SYSTEMS			
OMENTUM			
NECROSIS, FAT		1	1
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	3	1	4
ACCIDENTAL DEATH			1

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE ADMINISTERED FENTHION IN THE DIET

TABLE D1.
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE ADMINISTERED FENTHION IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	25	50	50
ANIMALS NECROPSIED	25	49	48
ANIMALS EXAMINED HISTOPATHOLOGICALLY	25	49	48
INTEGUMENTARY SYSTEM			
*SKIN	(25)	(49)	(48)
ABSCESS, NOS		2 (4%)	2 (4%)
ULCER, CHRONIC	1 (4%)		
HYPERPLASIA, NOS		1 (2%)	1 (2%)
RESPIRATORY SYSTEM			
*LUNG	(25)	(48)	(48)
ATELECTASIS		1 (2%)	
INFLAMMATION, FOCAL GRANULOMATOU		1 (2%)	
HEMATOPOIETIC SYSTEM			
*SPLEEN	(25)	(48)	(48)
HYPERPLASIA, FOLLICULAR-CELL			2 (4%)
HEMATOPOIESIS		1 (2%)	
*SPLENIC SINUSOIDS	(25)	(48)	(48)
HYPERPLASIA, NOS		1 (2%)	
*MANDIBULAR L. NODE	(21)	(43)	(42)
HYPERPLASIA, NOS		1 (2%)	
*MESENTERIC L. NODE	(21)	(43)	(42)
HYPERPLASIA, NOS		1 (2%)	
HYPERPLASIA, LYMPHOID	1 (5%)		
HEMATOPOIESIS		1 (2%)	
CIRCULATORY SYSTEM			
*PULMONARY ARTERY	(25)	(49)	(48)
HYPERTROPHY, FOCAL		1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#LIVER	(25)	(49)	(48)
INFARCT, NOS		1 (2%)	
INFARCT, ACUTE		1 (2%)	
METAMORPHOSIS FATTY			1 (2%)
FOCAL CELLULAR CHANGE		1 (2%)	1 (2%)
#PANCREAS	(25)	(47)	(48)
CYSTIC DUCTS			1 (2%)
#STOMACH	(24)	(45)	(42)
HYPERPLASIA, NOS			1 (2%)
#PEYERS PATCH	(24)	(43)	(40)
HYPERPLASIA, LYMPHOID			2 (5%)
URINARY SYSTEM			
#KIDNEY	(25)	(49)	(48)
INFLAMMATION, CHRONIC		1 (2%)	
HYPERPLASIA, LYMPHOID		1 (2%)	1 (2%)
#URINARY BLADDER	(22)	(44)	(41)
ATYPIA, NOS		1 (2%)	
METAPLASIA, SQUAMOUS	1 (5%)	1 (2%)	
ENDOCRINE SYSTEM			
#ADRENAL CORTEX	(21)	(48)	(46)
LIPOIDOSIS		1 (2%)	
#ADRENAL MEDULLA	(21)	(48)	(46)
HYPERPLASIA, NOS	1 (5%)		
REPRODUCTIVE SYSTEM			
NONE			
NERVOUS SYSTEM			
NONE			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(25)	(49)	(48)
HYPERPLASIA, LYMPHOID		2 (4%)	
HEMATOPOIESIS	1 (4%)		
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	13	7	16
ACCIDENTAL DEATH			1
AUTOLYSIS/NO NECROPSY		1	1

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D2.
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE ADMINISTERED FENTHION IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	25	50	50
ANIMALS NECROPSIED	24	47	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	24	47	50
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(24)	(46)	(50)
CONGESTION, NOS			1 (2%)
INFLAMMATION, INTERSTITIAL			1 (2%)
HYPERPLASIA, LYMPHOID			1 (2%)
HEMATOPOIETIC SYSTEM			
#SPLEEN	(24)	(45)	(48)
HEMOSIDEROSIS	1 (4%)		
HYPERPLASIA, LYMPHOID	2 (8%)	1 (2%)	2 (4%)
HEMATOPOIESIS		2 (4%)	
CIRCULATORY SYSTEM			
#HEART	(24)	(47)	(50)
PERIARTERITIS			1 (2%)
*CORONARY ARTERY	(24)	(47)	(50)
DEGENERATION, NOS			1 (2%)
HYPERPLASIA, NOS			1 (2%)
*HEPATIC ARTERY	(24)	(47)	(50)
PERIVASCULITIS		1 (2%)	
NECROSIS, NOS		1 (2%)	
DIGESTIVE SYSTEM			
#LIVER	(24)	(47)	(50)
GRANULOMA, NOS			1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
NECROSIS, COAGULATIVE		1 (2%)	
INFARCT, NOS	1 (4%)	1 (2%)	
METAMORPHOSIS FATTY		1 (2%)	1 (2%)
FOCAL CELLULAR CHANGE			1 (2%)
#LIVER/CENTRILOBULAR	(24)	(47)	(50)
NECROSIS, NOS		1 (2%)	
#PANCREAS	(22)	(45)	(48)
CYSTIC DUCTS	1 (5%)	2 (4%)	2 (4%)
#STOMACH	(24)	(44)	(41)
ATYPIA, NOS			1 (2%)
URINARY SYSTEM			
#KIDNEY	(23)	(47)	(48)
HYPERPLASIA, LYMPHOID	1 (4%)	5 (11%)	1 (2%)
#URINARY BLADDER	(18)	(41)	(39)
HYPERPLASIA, LYMPHOID			1 (3%)
ENDOCRINE SYSTEM			
#PITUITARY	(21)	(37)	(42)
HYPERPLASIA, NOS		1 (3%)	
#ADRENAL CORTEX	(23)	(45)	(46)
HEMORRHAGE		1 (2%)	
LIPOIDOSIS	1 (4%)		2 (4%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(24)	(47)	(50)
GALACTOCELE		1 (2%)	
DYSPLASIA, NOS			1 (2%)
#UTERUS	(19)	(45)	(40)
HYDROMETRA		1 (2%)	
#UTERUS/ENDOMETRIUM	(19)	(45)	(40)
HYPERPLASIA, CYSTIC		1 (2%)	4 (10%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
*OVARY	(24)	(40)	(43)
CYST, NOS	1 (4%)	2 (5%)	3 (7%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*EYE/LACRIMAL GLAND	(24)	(47)	(50)
HYPERPLASIA, ADENOMATOUS		1 (2%)	
MUSCULOSKELETAL SYSTEM			
*STERNUM	(24)	(47)	(50)
OSTEOPOROSIS		1 (2%)	
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(24)	(47)	(50)
HYPERPLASIA, LYMPHOID	1 (4%)	3 (6%)	2 (4%)
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	8	9	16
AUTOLYSIS/NO NECROPSY	1	3	

* NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

APPENDIX E

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS IN RATS ADMINISTERED FENTHION IN THE DIET

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered Fenthion in the Diet (a)

Topography: Morphology	Matched Control	Low Dose	High Dose
Integumentary System: Fibroma of the Skin (b)	2/25 (8)	0/50 (0)	0/49 (0)
P Values (c,d)	P = 0.036(N)	N.S.	N.S.
Relative Risk (f)		0.000	0.000
Lower Limit		0.000	0.000
Upper Limit		1.685	1.718
Weeks to First Observed Tumor	103	--	--
Hematopoietic System: Leukemia (b)	6/25 (24)	9/50 (18)	8/49 (16)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.750	0.680
Lower Limit		0.275	0.238
Upper Limit		2.317	2.154
Weeks to First Observed Tumor	98	77	96

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered Fenthion in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Pituitary: Carcinoma, NOS (b)	0/25 (0)	4/47 (9)	0/44 (0)
P Values (c,d)	N.S.	N.S.	--
Departure from Linear Trend (e)	P = 0.015		
Relative Risk (f)		Infinite	--
Lower Limit		0.506	--
Upper Limit		Infinite	--
Weeks to First Observed Tumor	--	80	--
Pituitary: Chromophobe Adenoma (b)	9/25 (36)	12/47 (26)	9/44 (20)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.709	0.568
Lower Limit		0.328	0.237
Upper Limit		1.668	1.418
Weeks to First Observed Tumor	73	79	84

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered Fenthion in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Thyroid: Follicular-cell Carcinoma (b)	0/23 (0)	2/44 (5)	0/27 (0)
P Values (c,d)	N.S.	N.S.	--
Relative Risk (f)		Infinite	--
Lower Limit		0.159	--
Upper Limit		Infinite	--
Weeks to First Observed Tumor	--	104	--
Thyroid: C-cell Adenoma (b)	2/23 (9)	5/44 (11)	3/27 (11)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.307	1.278
Lower Limit		0.238	0.161
Upper Limit		13.047	14.236
Weeks to First Observed Tumor	103	64	103

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered Fenthion in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Pancreatic Islets: Islet-cell Adenoma (b)	2/24 (8)	1/47 (2)	2/49 (4)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.255	0.490
Lower Limit		0.005	0.038
Upper Limit		4.703	6.476
Weeks to First Observed Tumor	98	96	94
Testis: Interstitial-cell Tumor (b)	18/24 (75)	37/50 (74)	45/49 (92)
P Values (c,d)	P = 0.028	N.S.	N.S.
Relative Risk (f)		0.987	1.224
Lower Limit		0.755	0.966
Upper Limit		1.405	1.521
Weeks to First Observed Tumor	98	86	83

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered Fenthion in the Diet (a)

(continued)

(a) Dosed groups received 10 or 20 ppm.

(b) Number of tumor-bearing animals/number of animals examined at site (percent).

(c) Beneath the incidence of tumors in the control group is the probability level for the Cochran-Armitage test when P is less than 0.05; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with the matched-control group when P is less than 0.05; otherwise, not significant (N.S.) is indicated.

(d) A negative (N) indicates a lower incidence in a dosed group than in the control group.

(e) The probability level for departure from linear trend is given when P is less than 0.05 for any comparison.

(f) The 95% confidence interval of the relative risk between each dosed group and the control group.

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Administered Fenthion in the Diet (a)

Topography: Morphology	Matched Control	Low Dose	High Dose
Hematopoietic System: Leukemia (b)	3/25 (12)	3/50 (6)	11/49 (22)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.500	1.871
Lower Limit		0.073	0.560
Upper Limit		3.524	9.741
Weeks to First Observed Tumor	85	70	94
Pituitary: Chromophobe Adenoma (b)	14/25 (56)	20/50 (40)	25/48 (52)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.714	0.930
Lower Limit		0.438	0.596
Upper Limit		1.277	1.586
Weeks to First Observed Tumor	79	79	76

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Administered Fenthion in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Thyroid: C-cell Adenoma (b)	2/22 (9)	12/48 (25)	4/46 (9)
P Values (c,d)	N.S.	N.S.	N.S.
Departure from Linear Trend (e)	P = 0.022 (N)		
Relative Risk (f)		2.750	0.957
Lower Limit		0.697	0.152
Upper Limit		23.940	10.075
Weeks to First Observed Tumor	105	104	102
Mammary Gland: Fibroadenoma (b)	1/25 (4)	6/50 (12)	1/49 (2)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		3.000	0.510
Lower Limit		0.399	0.007
Upper Limit		134.975	39.258
Weeks to First Observed Tumor	105	86	84

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Administered Fenthion in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Mammary Gland: Adenocarcinoma, NOS (b)	2/25 (8)	0/50 (0)	0/49 (0)
P Values (c,d)	P = 0.036 (N)	N.S.	N.S.
Relative Risk (f)		0.000	0.000
Lower Limit		0.000	0.000
Upper Limit		1.685	1.718
Weeks to First Observed Tumor	90	--	--
Uterus: Endometrial Stromal Polyp (b)	2/25 (8)	11/49 (22)	8/46 (17)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		2.806	2.174
Lower Limit		0.687	0.484
Upper Limit		24.758	19.975
Weeks to First Observed Tumor	83	74	44

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Administered Fenthion in the Diet (a)

(continued)

(a) Dosed groups received 10 or 20 ppm.

(b) Number of tumor-bearing animals/number of animals examined at site (percent).

(c) Beneath the incidence of tumors in the control group is the probability level for the Cochran-Armitage test when P is less than 0.05; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with the matched-control group when P is less than 0.05; otherwise, not significant (N.S.) is indicated.

(d) A negative (N) indicates a lower incidence in a dosed group than in the control group.

(e) The probability level for departure from linear trend is given when P is less than 0.05 for any comparison.

(f) The 95% confidence interval of the relative risk between each dosed group and the control group.

APPENDIX F

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS IN MICE ADMINISTERED FENTHION IN THE DIET

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Administered Fenthion in the Diet (a)

Topography: Morphology	Matched Control	Low Dose	High Dose
Integumentary System: Fibrosarcoma (b)	0/25 (0)	4/49 (8)	4/48 (8)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		Infinite	Infinite
Lower Limit		0.486	0.496
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	89	92
Integumentary System: Rhabdomyosarcoma (b)	0/25 (0)	3/49 (6)	2/48 (4)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		Infinite	Infinite
Lower Limit		0.315	0.158
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	61	68

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Administered Fenthion in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Integumentary System: Fibrosarcoma, Sarcoma, NOS, or Rhabdomyosarcoma (b)	0/25 (0)	7/49 (14)	8/48 (17)
P Values (c,d)	P = 0.043	P = 0.048	P = 0.028
Relative Risk (f)		Infinite	Infinite
Lower Limit		1.018	1.223
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	61	68
Lung: Alveolar/Bronchiolar Adenoma (b)	2/25 (8)	5/48 (10)	8/48 (17)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.302	2.083
Lower Limit		0.235	0.463
Upper Limit		13.059	19.178
Weeks to First Observed Tumor	104	78	92

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Administered Fenthion in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Hematopoietic System: Lymphoma or Leukemia (b)	1/25 (4)	6/49 (12)	2/48 (4)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		3.061	1.042
Lower Limit		0.407	0.058
Upper Limit		137.655	60.184
Weeks to First Observed Tumor	104	69	101
Liver: Hepatocellular Carcinoma (b)	6/25 (24)	15/49 (31)	13/48 (27)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.276	1.128
Lower Limit		0.548	0.467
Upper Limit		3.582	3.241
Weeks to First Observed Tumor	82	84	61

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Administered Fenthion in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Liver: Hepatocellular Carcinoma or Adenoma (b)	6/25 (24)	17/49 (35)	17/48 (35)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.446	1.476
Lower Limit		0.639	0.653
Upper Limit		3.980	4.055
Weeks to First Observed Tumor	82	84	61

(a) Dosed groups received 10 or 20 ppm.

(b) Number of tumor-bearing animals/number of animals examined at site (percent). Weeks to first observed tumor is based on time at death with tumor.

(c) Beneath the incidence of tumors in the control group is the probability level for the Cochran-Armitage test when P is less than 0.05; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with the matched-control group when P is less than 0.05; otherwise, not significant (N.S.) is indicated.

(d) A negative (N) indicates a lower incidence in a dosed group than in the control group.

(e) The probability level for departure from linear trend is given when P is less than 0.05 for any comparison.

(f) The 95% confidence interval of the relative risk between each dosed group and the control group

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Administered Fenthion in the Diet (a)

Topography: Morphology	Matched Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma (b)	3/24 (13)	3/46 (7)	3/50 (6)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.522	0.480
Lower Limit		0.076	0.070
Upper Limit		3.662	3.380
Weeks to First Observed Tumor	103	104	104
Hematopoietic System: Lymphoma (b)	6/24 (25)	12/47 (26)	13/50 (26)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.021	1.040
Lower Limit		0.416	0.433
Upper Limit		2.964	2.989
Weeks to First Observed Tumor	103	84	96

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Administered Fenthion in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Liver: Hepatocellular Carcinoma (b)	2/24 (8)	4/47 (9)	1/50 (2)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.021	0.240
Lower Limit		0.161	0.004
Upper Limit		10.779	4.429
Weeks to First Observed Tumor	103	104	96
Liver: Hepatocellular Carcinoma or Adenoma (b)	2/24 (8)	4/47 (9)	2/50 (4)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.021	0.480
Lower Limit		0.161	0.037
Upper Limit		10.779	6.350
Weeks to First Observed Tumor	103	104	96

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Administered Fenthion in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Pituitary: Adenoma, NOS, Acidophil Adenoma, or Chromophobe Adenoma (b)	0/21 (0)	3/37 (8)	4/42 (10)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		Infinite	Infinite
Lower Limit		0.354	0.481
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	100	103
Thyroid: Papillary Adenoma (b)	3/21 (14)	0/42 (0)	0/40 (0)
P Values (c,d)	P = 0.009 (N)	P = 0.033 (N)	P = 0.037 (N)
Departure from Linear Trend (e)	P = 0.036		
Relative Risk (f)		0.000	0.000
Lower Limit		0.000	0.000
Upper Limit		0.821	0.861
Weeks to First Observed Tumor	104	--	--

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Administered Fenthion in the Diet (a)

(continued)

(a) Dosed groups received 10 or 20 ppm.

(b) Number of tumor-bearing animals/number of animals examined at site (percent).

(c) Beneath the incidence of tumors in the control group is the probability level for the Cochran-Armitage test when P is less than 0.05; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with the matched-control group when P is less than 0.05; otherwise, not significant (N.S.) is indicated.

(d) A negative (N) indicates a lower incidence in a dosed group than in the control group.

(e) The probability level for departure from linear trend is given when P is less than 0.05 for any comparison.

(f) The 95% confidence interval of the relative risk between each dosed group and the control group.

APPENDIX G

ANALYSIS OF FORMULATED DIETS FOR CONCENTRATIONS OF FENTHION

APPENDIX G

Analysis of Formulated Diets for Concentrations of Fenthion

A 10-g sample from a formulated diet was shaken with 250 ml benzene for 3 hours. Sample aliquots of the extract were analyzed by gas chromatography using a flame photometric detector in the phosphorus mode.

Spiked samples were worked up simultaneously and the recoveries used to correct the recoveries from the dosed feed samples for losses due to the method.

Theoretical Concentration (ppm)	No. of Samples	Sample Analytical Mean (ppm)	Coefficient of Variation (%)	Range (ppm)
10	11	10.09	5.37	9.37-11.1
20	11	19.98	6.74	18.3-21.5

Review of the Bioassay of Fenthion* for Carcinogenicity
by the Data Evaluation/Risk Assessment Subgroup
of the Clearinghouse on Environmental Carcinogens

October 25, 1978

The Clearinghouse on Environmental Carcinogens was established in May, 1976, in compliance with DHEW Committee Regulations and the Provisions of the Federal Advisory Committee Act. The purpose of the Clearinghouse is to advise the Director of the National Cancer Institute (NCI) on its bioassay program to identify and to evaluate chemical carcinogens in the environment to which humans may be exposed. The members of the Clearinghouse have been drawn from academia, industry, organized labor, public interest groups, and State health officials. Members have been selected on the basis of their experience in carcinogenesis or related fields and, collectively, provide expertise in chemistry, biochemistry, biostatistics, toxicology, pathology, and epidemiology. Representatives of various Governmental agencies participate as ad hoc members. The Data Evaluation/Risk Assessment Subgroup of the Clearinghouse is charged with the responsibility of providing a peer review of reports prepared on NCI-sponsored bioassays of chemicals studied for carcinogenicity. It is in this context that the below critique is given on the bioassay of Fenthion for carcinogenicity.

The primary reviewer for the report on the bioassay of Fenthion said that the compound was not carcinogenic in either sex of treated rats or female mice, under the conditions of test. An increased incidence of sarcomas of the skin in treated male mice suggested that Fenthion was sarcomagenic in this sex and strain. The primary reviewer pointed out an increased but statistically insignificant incidence of leukemia and endometrial polyps in treated female rats.

The secondary reviewer of the bioassay of Fenthion recommended that the conclusion regarding the male mice be changed to read that the findings indicated the need for further study of Fenthion, and that the reference to the compound's carcinogenicity be deleted. He further suggested that the report contain literature references about the effects of fighting on subcutaneous sarcoma production in mice. The secondary reviewer concluded that Fenthion was not carcinogenic, under the conditions of test, and he recommended that the compound be retested by subcutaneous injection into an appropriate species.

A Program staff pathologist noted the increased incidence of rhabdomyosarcomas observed among treated male mice. He said that this was a relatively rare tumor in historical control animals.

There was no objection to a recommendation that the report be accepted as written.

Clearinghouse Members Present:

Arnold L. Brown (Chairman), University of Wisconsin Medical School
Joseph Highland, Environmental Defense Fund
William Lijinsky, Frederick Cancer Research Center
Henry Pitot, University of Wisconsin Medical Center
Verne A. Ray, Pfizer Medical Research Laboratory
(Michael B. Shimkin, University of California at San Diego, submitted a written review)
Kenneth Wilcox, Michigan State Health Department

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* Subsequent to this review, changes may have been made in the bioassay report either as a result of the review or other reasons. Thus, certain comments and criticisms reflected in the review may no longer be appropriate.

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